REMARKS

Upon entry of the present amendments, claims 1-3, 6-8, 11-23, 25-27, 30-35, 37-39, 42, 43, and 52-56 will be pending. Claims 4, 5, 9, 10, 24, 28, 29, 36, 40, 41, and 44-51 have been canceled. Applicants have amended claims 1, 15, 16, 17, 23, 32, 52, and 53. Support for the amendments can be found throughout the specification, for example, at page 6, line 34 to page 7, line 1; page 9, lines 8-9; page 10, lines 16-17; page 13, lines 26-28; page 14, lines 28-30; page 24, lines 25-26; page 41, lines 11-12; and in the Examples. No new matter has been added.

Information Disclosure Statement

Applicants thank the Office for considering the references disclosed in the IDS filed October 31, 2007.

Priority

According to the Office, this application claims the benefit of priority from U.S. Pat. Application 07/855,562 filed March 23, 1992. However, also according to the Office, "... the parent, US-PAT 5,643,578, does not have benefit of (1) retroviral promoter, (2) SIV antigen, (3) rotavirus antigen, (4) microsphere encapsulation of DNA, (5) methods of immunization comprising combinations of influenza antigens. Therefore these limitations will be given the benefit of US-PAT 6,841,381, filed on 27 January 1994."

While applicants acknowledge that the Office is mostly correct, applicants submit that support for "retroviral promoter" can indeed be found in U.S. Pat. Application 07/855,562 and U.S. Pat. No. 5,643,578 (" the '578 patent"). It is well known in the art that the retroviral promoter is part of the long terminal repeat (LTR), which contains all of the elements necessary for gene expression. Both the '578 patent and 07/855,562 disclose (e.g., Example 1, and Figs. 1 and 2) two vectors, pP1/H7 and p188, each encoding an influenza virus antigen. As evident from Figs. 1 and 2 from both of these references, the vectors pP1/H7 and p188 each includes at least two LTR's. Thus, skilled practitioners would have understood that the '578 patent and 07/855,562 describe a retroviral promoter. Accordingly, applicants submit that the element

"retroviral promoter" recited in the instant claims is entitled to the benefit of priority of 07/855,562 filed March 23, 1992.

Withdrawn Rejections

Applicants note with appreciation that the Office has withdrawn (Office Action at pages 3-6) various rejections under 35 U.S.C. § 102(b), obviousness-type double patenting, and 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, Second Paragraph

The Office rejected claim 17 as being indefinite because the term "plasmid vector" lacks proper antecedent basis.

Applicants have amended claim 17 to recite "the plasmid vectors." Withdrawal of this rejection is respectfully submitted.

35 U.S.C. § 112, First Paragraph

The Office rejected claims 1-4, 6-8, 11-23, 25-27, 30-35, 37-39, 42, 43, and 52-56 as allegedly failing to comply with the written description requirement on various grounds.

The Office asserted (Office Action at pages 7-8) that the specification provides no literal support for the phrase "consisting essentially of" recited in the claims. Applicants respectfully disagree and traverse. As an initial matter, applicants respectfully note that the phrase "consisting essentially of," like "comprising," is a transitional phrase with a well-established meaning in patent law. It is not terminology that requires description in the specification. Further, with respect to the written description requirement, MPEP § 2163 (I)(B) states: "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure (emphasis added)." Thus, contrary to what the Office appears to suggest, literal support is not required to satisfy the written description requirement. Skilled practitioners, reading the specification in its entirety, could readily appreciate that the basic inventive concept of applicants' method is drawn to, *inter alia*,

direct inoculation of DNA to subjects for immunization. As such, the present method includes administering a composition that requires no more than DNA in a physiologically acceptable medium suitable for introducing DNA to a subject (see the specification, e.g., at page 9, lines 22-24), although the composition could include other elements that do not materially change the basic and novel characteristics of the method. In any event, the specification contains ample description of a composition consisting essentially of plasmid vectors in a physiologically acceptable medium. For example, the specification clearly describes (e.g., at page 14, lines 28-30; page 24, lines 21-22; and page 27, lines 1-2) administering plasmid vectors in saline to animal models, saline being a physiologically acceptable medium (see the specification, at page 9, lines 23-24). Thus, the instant claims are adequately described, and the transitional phrase "consisting essentially of" is not "new matter."

The Office also contends that there is no literal support for the phrase "a set of plasmid vectors." Applicants respectfully disagree, but for the sole purpose of expediting prosecution of this application, applicants have amended the claims to recite "a plurality of the same plasmid vectors." The specification provides extensive description of compositions including a plurality of the same plasmid vectors in a physiologically acceptable medium. For example, the specification discloses (e.g., at page 14, lines 28-30; and page 24, lines 25-26) administering the vector pP1/H7 alone in saline, or pCMV/H1 alone in saline to animal models. Applicants note that skilled practitioners could readily appreciate that, in each of these instances, a number (e.g., a plurality) of the same plasmid vectors, rather than one single plasmid vector, is administered. Accordingly, the specification provides adequate written description for a plurality of the same plasmid vectors.

The Office further asserts that the phrase "two or more sets of plasmid vectors" is not supported. Applicants again disagree. However, for the sole purpose of expediting prosecution of this application, applicants have amended the claims to recite "a mixture of plasmid vectors." The specification describes (e.g., at page 10, lines 16-17) using a mixture of DNA, e.g., plasmid vectors, for vertebrate immunization.

Lastly, the Office states that the specification lacks support for a composition consisting essentially of a set of microsphere encapsulated plasmid vectors." Applicants have amended the claims to recite "a composition consisting essentially of a plurality of the same microsphere encapsulated plasmid vectors." The phrase "consisting essentially of" is supported by the specification as filed for the reasons stated above. Furthermore, the specification describes (e.g., at page 41, lines 11-12) administering a plurality of the same microsphere encapsulated plasmid vectors (e.g., alginate-encapsulated pCMV/H1 alone) in water to mice, and therefore provides support for the recited composition.

In view of the foregoing, applicants submit that the instant claims comply with the written description requirement. Reconsideration and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

The Office rejected claims 1-4, 6-8, 11-23, 25-27, 30-35, 37-39, 42-43, 52-56 as allegedly obvious over Felgner et al. (WO90/11092; "Felgner") in view of Huylebroeck et al. (Gene, June 1988, 66(2): 163-81; "Huylebroeck"), Townsend et al. (Cell, November 1984, 39(1): 13-25), Atkinson et al. (U.S. Pat. No. 4,861,864; "Atkinson"), and Andrianov et al. (U.S. Pat. No.5,529,777; "Andrianov").

According to the Office (at pages 10-11):

> Felgner et al. teach plasmid vectors comprising "therapeutic polynucleotides ... [which] code for immunity-conferring polypeptides, which act as endogenous immunogens to provoke a humoral or cellular response, or both" ... Huylebroeck et al. teach plasmid DNA mediated gene transfer of two different influenza A antigens, including H1 hemagglutinin (abstract) ... Townsend et al. teach plasmids comprising hemagglutinin antigens ... Atkinson et al. teach a plasmid comprising cDNA of a rotavirus antigen for expression of VP7 ... Andrianov et al. teach "polymeric hydrogels are used to encapsulate antigen to form vaccines ... microparticles are formed ....preferred polymers are alginate" (abstract) and "enhanced immunogenicity of microspheres formed of 95% alginate" .... Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the

combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

The Office appears to suggest that, because plasmids encoding an influenza virus antigen or a rotavirus antigen were known, and Felgner suggests the general concept of DNA vaccine, it would have been predictable that direct administration of these plasmids to a subject would successfully immunize the subject against a subsequent infection. Applicants disagree and traverse. Applicants submit that none of references, individually or combined, suggest that a DNA vaccine could be used successfully to protect a subject from a subsequent viral infection. Thus, even assuming that skilled practitioners would have been led to combine the teachings of these references, the instant claims would not have been obvious, as there would have been no reasonable expectation of success.

In contrast, the present specification demonstrates protective immunization against, for example, influenza via multiple routes of administration (e.g., intramuscular, intravenous, intraperitoneal, subcutaneous, intradermal, and intranasal; see, e.g., Examples 1, 3, 4, 5, 6, and 9) and in multiple model systems (e.g., chickens and mice). As stated in the specification (at page 7, lines 9-11), "...a vertebrate immunized by the present invention will not be infected or will be infected to a lesser extent than would occur without immunization (emphasis added)." In other words, applicants' plasmid vectors did not merely induce antibody responses or treat existing infections. Rather, the induced protective immune responses protected immunized animals against subsequent challenges with otherwise lethal doses of influenza virus, as required by the instant claims.

Before we discuss Felgner further, we remind the Examiner of the meaning of the phrase "protective immune response" as recited in the claims. A protective immune response is an immune response, e.g., a humoral immune response or a cell-mediated immune response induced by an antigen, that protects (partially or totally) an immunized subject from subsequent infection by an infectious agent. This type of prophylactic response is very different from a treatment of an existing viral infection, and is not at all obvious from such a therapeutic treatment.

While Felgner generally discloses the introduction of DNA or RNA into vertebrates for a variety of applications, including so-called immunization, applicants have found no actual data in

Felgner to suggest that DNA vaccines can be used to successfully immunize a subject against infection from an influenza virus or a rotavirus.

Whatever data Felgner discloses regarding DNA immunization are limited to HIV, and none of the data demonstrate that any DNA vaccine can confer protective immunity against a viral infection. In Example 9, Felgner describes injecting HIV-infected mice with a liposome formulation containing RNA encoding the HIV *nef* protein, and assaying the anti-viral effect of blood samples obtained from the treated mice. While Example 9 states that mice can be treated with *nef* RNA, and then subsequently challenged with the HIV virus, there is no actual data showing that such treatment can effectively protect mice from a subsequent HIV infection. In fact, according to Felgner (at page 57, lines 24-25), "... these results indicate a moderate anti-viral effect of the (*in vivo*) treatment (*emphasis added*)." Thus, aside from the fact that Felgner uses RNA, not DNA, there is no suggestion here that administration of nucleic acids encoding a viral protein can confer protective immunity against a subsequent viral infection. In other words, Felgner describes the partial effectiveness of its methods for treating an existing HIV infection, but no data whatsoever to show that the methods can work to vaccinate a healthy subject to provide protective immunity against a later infection.

Similarly, in Example 19, although Felgner discloses that antibodies against gb-120 were detected in the blood of mice injected with a construct encoding gp-120, there is no data to show that the construct can protect these mice from an HIV infection that begins after immunization. Felgner merely concludes (at page 70, lines 34-36): "The study indicates that the gene retains its signal sequence, and the protein is efficiently excreted from cells." There is also no suggestion here that administration of such a DNA construct as a vaccine to a subject can protect the subject from a subsequent HIV infection. The Office has not pointed to any evidence to show that skilled practitioners would have expected a DNA vaccine to be successful based on the disclosure of Felgner. Thus, not only does Felgner fail to disclose DNA vaccine against an influenza virus or a rotavirus, reading the reference, skilled practitioners also would not have expected a DNA vaccine to successfully immunize a subject against viral infection.

Huylebroeck does not remedy the deficiencies of Felgner. This reference discloses plasmid vectors for transient expression of DNA in animal cells (see, e.g., Abstract), and using these vectors to express influenza hemagglutinin HA in cultured cells (see, e.g., at page 173, right column). According to Huylebroeck (at page 179, right column, second paragraph), these vectors are useful tools because "... [transient] expression is a valuable and rapid system for investigating polypeptide regions responsible for various properties of viral antigens, in particular the immunogencity, receptor-binding, enzymatic or fusogenic activities of membrane-bound glycoproteins ... (emphasis added)." There is nothing here that would have lead skilled practitioners to use these vectors to immunize vertebrate against later influenza infections. This concept of using expression vectors as tools to study polypeptides expressed *in vitro* differs markedly from the concept of administering DNA directly to a subject for expression *in vivo* for immunizing the subject. As Huylebroeck does not even suggest the concept of DNA vaccines, it provides no further information regarding DNA vaccination to supplement the disclosure of Felgner. Accordingly, even assuming that skilled practitioners would have combined the teachings of Felgner and Huylebroeck, skilled practitioners would not have had a reasonable expectation that a vector encoding a viral antigen could be used successfully as a vaccine. Thus, the instant claims would not have been obvious over Felgner and Huylebroeck, individually or combined.

The Office also cites Townsend, but this reference also fails to rectify the deficiencies of Felgner and Huylebroeck. Townsend (at page 13, right column, the first full paragraph) used established cell lines expressing individual influenza genes "... to compare the roles played by the nucleoprotein and hemagglutinin molecules in target cell recognition by influenza A specific cytotoxic T cells." Like Huylebroeck, using transfected cells to study viral proteins *in vitro* does not provide any suggestion for a DNA vaccine that provides a protective immune response. The Office (at page 11 of the Office Action) cites Townsend for disclosing plasmids encoding hemagglutinins and routine isolation of influenza genes. However, the mere ability to construct a plasmid expressing an influenza gene is not the same as the ability to use the plasmid as an effective DNA vaccine against subsequent influenza infections. The Office (at page 11 of the

Office Action) further points to Townsend for suggesting a vaccine that presents nucleoprotein in an appropriate form. While Townsend does make such a suggestion, it does so in the context of a discussion on whether cytotoxic T cells can also recognize denatured peptides presented on the cell surface, and not only viral antigens in their native conformation (see page 22, right column, the first two paragraphs). Applicants fail to see why this discussion would have led skilled practitioners to any DNA vaccine, much less the expectation that a DNA vaccine would successfully immunize a vertebrate. In view of the foregoing, Townsend would not have led skilled practitioners to a method for immunizing a subject by direct administration of DNA to the subject. Furthermore, like Felgner and Huylebroeck, it also fails to provide a reason for skilled practitioner to reasonably expect that such a method would be successful. Accordingly, these three references, individually or combined, do not render the instant claims obvious.

Nor does Atkinson remedy these deficiencies of Felgner, Huylebroeck, and Townsend. The Office (at page 12 of the Office Action) is correct that Atkinson discloses plasmids encoding the rotavirus antigen VP7, and its purpose to provide a neutralizing antigen readily disseminated throughout the body. However, according to Atkinson (e.g., at column 2, line 66, to column 3, line 2), this purpose is achieved by making mutant VP7 polypeptides that can be used as a vaccine. Atkinson describes using VP7-encoding plasmids for producing VP7 polypeptides, or studying the properties of various VP7 mutant polypeptides in cultured cells transfected with these plasmids (e.g., at column 8, lines 50-55; column 9, lines 10-15; and column 10, lines 26-30). The reference further describes making cell lines or yeast strains that stably express the VP7 polypeptides as sources of these polypeptides (e.g., at column 3, lines 3-9; and column 12, lines 45-49). Thus, there is nothing in Atkinson to suggest a DNA vaccine. Since the reference does not even mention the concept of DNA vaccination, it would not have led skilled practitioners to expect that a DNA vaccine would confer protective immunity against a viral infection. Since none of Atkinson, Felgner, Huylebroeck, and Townsend shows that DNA vaccine could protect a subject from viral infection, even if skilled practitioners would have been led to combine these references, they would not have reasonably expected that DNA vaccine could be used successfully.

The Office further cites (at page 12 of the Office Action) Andrianov for teaching using polymer encapsulated antigen to form a vaccine and using the polymer to deliver nucleic acid encoding an antigen to cells. As an initial matter, applicants note that Andrianov has an earliest possible filing date of July 12, 1993. On the other hand and as noted above, the present application has a priority date of March 23, 1992, except with respect to the following elements: SIV antigen, rotavirus antigen, microsphere encapsulated DNA, and methods of immunizing using DNA encoding different influenza antigens. Andrianov does not appear to disclose or suggest any of these elements, except for microsphere encapsulated DNA, and the Office seems to cite this reference only for that disclosure. While encapsulating DNA is one useful way to administer the DNA to a subject, it is not necessary for formulating an effective DNA vaccine, as demonstrated by the examples described in the specification. The instant claims are novel and non-obvious, because at the time of filing, skilled practitioners would not have reasonably expected a DNA vaccine to successfully immunize a subject. As Andrianov can only be cited against the use of microsphere encapsulated DNA, it does not provide any information to supplement the teachings of Atkinson, Felgner, Huylebroeck, and Townsend to render the instant claims obvious. Accordingly, the instant claims would not have been obvious over Atkinson, Felgner, Huylebroeck, Townsend, and Andrianov, individually or combined.

In view of the above, even assuming that skilled practitioners would have been led to combine the teachings of all of the cited references, contrary to the Office assertion, they would not have had a reasonable expectation that direct administration of DNA encoding a viral antigen to a subject could successfully immunize the subject against a later viral infection. Thus, the instant claims would not have been obvious. Applicants respectfully request that this rejection be reconsidered and withdrawn..

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The $525 fee for a three-month extension is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-217002.

Respectfully submitted,

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